

REMARKS

Reconsideration of this application is respectfully requested. Claim 14 is currently pending.

Rejection Under 35 U.S.C. § 103

Claim 14 was rejected under 35 U.S.C. § 103 as obvious over U.S. 6,136,956 to Kogiso *et al.* or JP-B-3012932, also to Kogiso (both discussed collectively as “Kogiso”) in view of U.S. Patent No. 6,743,638 to Tsilosani *et al.* (“Tsilosani”) for the reasons discussed on pages 2-6 of the Office Action. Applicants respectfully traverse the rejection for the reasons that follow.

1. Applicants respectfully submit that the combination of Kogiso and Tsilosani clearly fails to meet the *prima facie* test for obviousness for at least the following reasons. To begin with, the combination of Kogiso and Tsilosani fails to teach or suggest all elements of claim 1. As noted in the previous amendment and response filed on July 20, 2007 and April 07, 2008, Kogiso does not teach or suggest several features of pending claim 14. Importantly, Kogiso does not teach or suggest “*a fine spherical body having a nearly spherical shape with a particle diameter of from 5 μ m to 15 μ m*”. Nor does Kogiso teach or suggest a hydrophilic core substance encapsulated inside the fine spherical body wherein the microcapsule has a uniform molecular orientation that when observed using a fluorescent microscope, emits fluorescence owing to pyranine as the inclusion compound.

In contrast to claim 14, Kogiso teaches a fine fibrous assembly having a molecular structure of a bola-form peptide lipid containing L- or D- valine residues. *See*, Kogiso abstract. Further, Kogiso teaches generally in the background section that spherical assemblies obtained from a natural phospholipid or so-called liposomes are known among molecular aggregates formed from a phsopholipid. *See*, Kogiso, col. 1, ll. 21-23. Kogiso's primary object is to obtain fine fiber assembly of a peptide having a length of several micrometers and a diameter of several tens of nanometers, which could not be obtained in the prior art from a natural phospholipid. *See*, Kogiso col. 1, ll. 45-50. However, considering Kogiso as a whole, he does not teach or suggest that a “spherical body” or “microcapsule” can be obtained or prepared from the novel peptide of formula 1 of the present invention. Also, Kogiso does not teach or suggest that a

hydrophilic core substance can be encapsulated within that spherical body. Thus, Kogiso fails to teach several elements of claim 14.

Additionally, Applicants respectfully disagree with the assertion in the Office Action that “this known (PRODUCT) could have been into a spherical microcapsule (PRODUCT) or any other PRODUCT, known at the time of the invention.” *See*, Office action at page 3. First, it was not known at the time of the invention that the lipid molecule of formula 1 could have been aggregated into a spherical microcapsule. The lipid molecule could have been in any number of possible shapes such as rod like, plate like, membrane like, vesicle like and so on. Second, Applicants did not achieve the spherical microcapsule simply by performing routine experimentation. Rather, Applicants deliberately and inventively pursued creating the microcapsule of the present invention by performing research into the self assembly process. *See*, specification at page 10. The Applicants discovered that when metal salt of bicephalic peptide and a hydrophilic core substance are used, the compound self-assembles under certain conditions to produce a spherical microcapsule encapsulating the hydrophilic core substance. *Id.* Third, even if the basic molecular structure is the same as that of Kogiso, Applicants here are claiming a *different product*, which is a spherical body, with different physical, structural, and chemical properties from that of the basic building block, *i.e.*, structure of formula 1. The patentability of this invention lies not with the structure of formula 1, but with the spherical body with uniform molecular orientation, evenly oriented in a radial pattern from a center, and a concentric molecular orientation having a point disclination. Thus, this spherical body is not the same entity as the structure of formula 1 in the same way as a cell is not the same thing as an organ. Accordingly, Applicants respectfully submit that Kogiso does not teach all elements of claim 14.

Similarly, Tsilosani also fails to teach all elements of claim 14, and, importantly, fails to fill in the deficiencies of Kogiso. Specifically, Tsilosani fails to teach the structure recited in claim 1, *i.e.*, the symmetrical peptide lipid molecule as represented by formula 1. Formula 1 has a symmetrical structure across a hydrophobic linear alkyl group in which hydrophilic peptide groups are substituted at the ends of the hydrophobic linear alkyl group. In contrast to formula 1, Tsilosani describes utilizing a *phospholipid liposome* as a stimuli-responsive microcapsule. *See*,

e.g., Tsilosani, col. 13, line 66 – col. 14, line 5. Further, Tsilosani teaches in Example 1, liposomes that encapsulate a pyranine. *See*, Tsilosani, col. 15, ll. 11-32.

As is well known in the art and has been recognized by Kogiso in the background section, liposome is a spherical self-organized matter containing a phospholipid as a constitutional molecule. It is defined as a simple model of a cell (membrane). The phospholipid, as a constitutional molecule, is a generalized amphipathic compound, an example of which includes phosphatidyl choline. However, Tsilosani fails to teach or suggest that the microcapsule comprises a compound of formula 1 and that the “*microcapsule has a uniform molecular orientation, evenly oriented in a radial pattern from a center, and a concentric molecular orientation having a point disclination*” as recited in claim 14. Additionally, the natural phospholipids forming the liposome as taught by Tsilosani form a molecular aggregate having a ***different overall structure*** from that formed with the peptide lipid molecule of formula (1) as discussed in detail *infra*.

Therefore, the combination of Kogiso and Tsilosani fails to teach or suggest all of the limitations of claim 14. Even if Kogiso and Tsilosani are combined, it is impossible for a person of skill in the art to foresee that the spherical aggregate of a liposome as taught in Tsilosani can be obtained from the bicephalic peptide compound described in Kogiso. Accordingly, Applicants respectfully request withdrawal of this rejection.

2. Moreover, Applicants respectfully submit that there is no suggestion or motivation in either Kogiso or Tsilosani to modify the references to arrive at the invention of claim 14.

To reach a proper teaching of a process or composition through a combination of references, there must be stated in the references (or shown in the knowledge generally available in the art) an objective motivation to combine the teachings of references, not a hindsight realization in light of the disclosure of the specification being examined. *See* MPEP 2143 and 2143.01; *In re Fine*, 5 USPQ.2d 1596, 1598 n.1 (Fed Cir 1988) (“The PTO has the burden under section 103 to establish a *prima facie* case of obviousness...It can satisfy this burden only by

showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the prior art to deprecate the claimed invention.” See, also *In re Lakowski*, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989) *W. L. Gore & Assoc. v. Garlock*, 220 USPQ 303, 311-13 (Fed. Cir. 1983); *Ex Parte Levengood*, 28 U.S.P.Q.2d 1300 (Board of Appeals and Interferences, 1993); *Ex Parte Chicago Rawhide Mfg. Co.*, 223 U.S.P.Q. 351 (Board of Appeals and Interferences, 1984). The teaching or suggestion to combine and the reasonable expectation of success must be found in the prior art, and not in the applicants’ disclosure. *Id.* at 493. See, also MPEP §2142. Recently, the Supreme Court has held that while the teaching-suggestion-motivation (TSM) test should not be applied rigidly, it still remains necessary to identify a reason that would have prompted a person of ordinary skill in the art to combine elements from the prior art as the new invention does. *KSR v. Teleflex*, 550 U.S. 398 (2007, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007)). Applicants respectfully submit that the references of Kogiso and Tsilosani cited in the Office Action fail to meet the tests prescribed by the Federal Circuit and the Supreme Court as discussed below.

In this rejection, no objective basis was established for combining the teachings of the references; instead, a selection of helpful portions from each reference was made while ignoring the unhelpful portions. Applicants submit that the use of liposomes was well known in the art. In fact, liposome can be easily obtained by treating a suspension of a phospholipid. However, it is also well known in the art that the structure of the aggregate so formed is different depending on the structure of the lipid. For example, the following references, attached herewith in an IDS form, indicate that the structure of the spherical body is different depending on the type of lipid that is used.

A.D. Bangham and R.M.C. Dawson, *Nature* (1958) 182, 1292-1293

A.D. Bangham, *Nature* (1961) 192, 1197-1198

A.D. Bangham and R.W. Horne, *Nature* (1962) 196, 952-953.

From reading Bangham, it is clear to one of skill in that art that it is difficult to predict the structure of the aggregate of the bicephalic peptide compound as shown in formula 1. If a person of skill in the art were to predict the structure based on the lipid of formula 1, it is more likely

that the person would predict a plate-like aggregate structure. However, it would have been difficult, if not impossible, for that person of skill to predict a spherical body (microcapsule) based on the structure of the lipid of formula 1. This is because the structure of formula 1 is a symmetrical lipid molecule with two polar head groups, which are linked to either end of the hydrophobic chain. See, structure in claim 14. In contrast, a *phospholipid* as taught by Tsilosani contains one polar head group and an apolar tail group. Given the structural differences between formula 1 and a phospholipid molecule, a person of ordinary skill in the art would be unable to predict the three-dimensional structure based only on the structure of formula 1. At least some degree of predictability is required from the prior art, and here, such prediction of the shape of the three dimensional structure is lacking based on Tsilosani. See, also MPEP 2143.02.

3. Additionally, Applicants submit that the prior art can be modified as *prima facie* obvious as long as there is a reasonable expectation of success. In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). There is nothing in Tsilosani to indicate that the lipid of formula 1 produces a spherical body, a microcapsule, a molecular membrane or fibers. Moreover, as shown in "Intermolecular and Surface Forces" by J.N. Israelachvili, Academic Press, London, 1985, which was submitted in the response filed on April 7, there is a correlation between the forms of packing of amphipathic compounds and the structure formed by them. It is known in the art that the phospholipid reported by Tsilosani forms a vesicle structure (liposome) owing to the critical packing structure and the packing parameter thereof. See, *id.*, wherein the critical packing shape is in the form of a truncated cone. In contrast, the compound of the present application has a critical packing structure in a cylindrical form, *i.e.*, the packing parameter is approximately "1". See, *id.*, wherein the critical packing shape is in the form of a truncated cone. Therefore, using the lipid of formula 1, a person of skill in the art would expect to produce only a planar molecular membrane and would not expect that it is capable of forming a vesicle structure which is a flexible molecular membrane.

However, by analyzing in detail the mechanism of forming organized matter, the Applicants found that the compound of the present application forms a vesicle structure as an intermediate, and further found that it can be produced as a spherical organized matter by subjecting the intermediate compound to an interaction with a surface-treated substrate. See,

specification at page 10 regarding details on method of preparation of the spherical microcapsule. Although Kogiso has shown that the structure of formula 1 forms a fibrous structure, it was not known that the structure of formula 1 can form spherical particles. Just because a known basic structural component can form a three dimensional fibrous structure as shown by Kogiso, it does not follow that the same structural component can also form a spherical body or a membrane. Here, Applicants have achieved a spherical body (microcapsule), which is unexpected and surprising result in that the structure of a spherical body using the lipid of formula 1 was not predictable or expected based on the prior art. Thus, absent a reasonable *expectation of success or the desirability* of obtaining the spherical body based on Kogiso and Tsilosani, the invention of claim 14 cannot be held obvious. Accordingly, Applicants respectfully request withdrawal of this rejection.

Reconsideration with allowance is thus respectfully requested.

No additional fees are believed to be required for this submission. Should any fees be required, however, please charge those fees to Morgan, Lewis & Bockius LLP deposit account no. 50-0310.

Respectfully submitted,

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Dated: February 25, 2009

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